Comparison of Clinical, Ultrasonographic, and Biochemical Differences at the Beginning of Puberty in Healthy Girls Born Either Small for Gestational Age or Appropriate for Gestational Age: Preliminary Results

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Context: There are limited and controversial data concerning puberty characteristics in girls born small for gestational age (SGA).

Objective: The objective of the study was to document clinical, ultrasonographic, and biochemical characteristics at the beginning of puberty in matched healthy girls born either SGA or appropriate for gestational age (AGA) recruited from the community.

Patients: Inclusion criteria were breast Tanner stage II and a body mass index between the 10th and 95th percentiles.

Interventions: Recruited subjects underwent a complete physical exam, bone age, and ultrasound measurements of the internal genitalia. Hormonal assessment included fasting early morning dehydroepiandrosterone sulfate, androstenedione, SHBG, inhibin-B, FSH, LH, estradiol (E2), 17-hydroxyprogesterone (17OH Prog), and testosterone. Thereafter, a GnRH agonist test (leuprolide 500 μg, sc) was performed with FSH and LH at time 3 and 24 h for E2, 17OH Prog, and testosterone.

Results: Sixty-five girls (35 AGA, 30 SGA) with a mean age of 9.9 $\pm$ 1.03 (7.8–12.5) yr, similar bone age/chronological age (1.02 $\pm$ 0.8 in AGA and 1 $\pm$ 0.76 in SGA), median height of 1.35 $\pm$ 0.06 cm, and similar waist to hip ratio were included. No differences in the presence of pubic hair, axillary hair, apocrine odor, or ultrasound measurements were found. SGA girls had increased baseline E2 as well as stimulated E2 and 17OH Prog.

Conclusions: In a preliminary sample of lean, healthy girls recruited from the community born either SGA or AGA, we observed slight hormonal differences at the beginning of puberty. Longitudinal follow-up of this cohort will allow us to understand whether these differences are maintained and have a clinical impact in their pubertal development.

CHILDREN BORN SMALL for gestational age (SGA) are at higher risk for perinatal morbidity, mortality, and a number of chronic diseases in later life, such as glucose intolerance, type 2 diabetes mellitus, and cardiovascular disease. The hallmark for these conditions seems to be decrease in insulin sensitivity (1).

The general accepted hypothesis explaining the development of these long-term alterations relates to the thrifty phenotype as an adaptive response to intrauterine malnutrition and modifications thereof; called "fetal origins" and recently updated to "developmental origins," these include the additional contributions of the growth patterns in infancy and childhood (2–4).

There are still limited data concerning the effects of being born SGA on the gonadal axis (5). Most of these studies have been performed in a selected cohort (northern Spanish girls), are cross-sectional in design, and show that reduced fetal growth appears to be associated with exaggerated adrenarche (6, 7), early puberty (8), and small ovarian and uterine size (9), with subsequent development of ovarian hyperandrogenism (10).

Studies concerning the timing, duration, and progression of puberty in children born SGA are remarkably scarce, and more importantly the results are difficult to compare due to the various methodologies, definitions, follow-up periods, and inclusion criteria (11–13). Several authors agree that in children born SGA, puberty appears to start at a normal age or slightly earlier but may have a more rapid progression compromising adult height (11, 14). Phillip and colleagues (11) in Israel and Carrascosa and colleagues (15) in Spain reported that children born SGA who were persistently short had a normal pubertal course with a distinct pubertal growth pattern, compromising final height when compared with their target height.

Because data regarding complete pubertal development and gonadal function in a nonselective SGA cohort followed up prospectively are unavailable, we decided to recruit lean, healthy girls, born either SGA or appropriate for gestational age (AGA) from the community and study their clinical, ultrasonographic, and biochemical characteristics of pubertal development.

Abbreviations: AGA, Appropriate for gestational age; BA, bone age; BMI, body mass index; CA, chronological age; DHEA-S, dehydroepiandrosterone sulfate; FAI, free androgen index; 17OH Prog, 17-hydroxy progesterone; SGA, small for gestational age.

Subjects and Methods

Subjects

A prospective study was designed by age matching girls between 7 and 12 yr old who attend public schools in the cities of Santiago and Concepción in Chile. They were invited to participate in a study of the impact of birth weight on pubertal progression and gonadal function. In addition, we used different local media to encourage participation in the study (school meetings for parents, local newspapers, magazines, and radio stations).

All girls were evaluated at the Institute of Maternal and Child Research with a complete physical exam performed by one pediatric endocrinologist (A.M.). Data from the newborn period were reported by the parents and confirmed in the child's health control card. We documented birth weight, length, and gestational age. Birth weight was classified as AGA when ranged between the 10th and 90th percentiles and SGA when the range was below the 10th percentile for the Chilean population adjusted for gender and gestational age (16, 17).

Inclusion criteria were good health (by medical history and physical examination), Tanner stage II of breast development according to the criteria of Tanner (18), and a body mass index (BMI) between the 10th and 95th percentiles (19). None of the girls was receiving medication that could interfere with growth or development.

Study protocol

At baseline, we obtained hand x-rays to determine bone ages by the method of Greulich and Pyle (20) performed by a single observer who was blinded to the patient status.

After an overnight fast, the subjects underwent a complete physical examination by a pediatric endocrinologist. Height and weight were measured by one nurse (A.A.). Height was measured using a wall-mounted Harpenden stadiometer (Holtain, UK). Weight was measured using a manual scale with a 10-g gradation (Seca; Quickmedical, Snoqualme, WA). Pubertal development was assessed according to the method of Marshall and Tanner (21). Hirsutism was evaluated by determining the presence of terminal hair using the modified Ferriman-Gallway score (22). The presence of acne was also determined. Waist and hip circumferences were measured to the nearest 0.5 cm using a flexible measuring tape by a single observer (T.C.). Waist was defined as the narrowest circumference between the inferior costal margin and the iliac crest in the standing position. The hip circumference measurement was obtained at the maximum perimeters at the level of the femoral trochanters.

Thereafter all the individuals underwent a GnRH test with 500 μg of leuprolide acetate injected sc as previously described (23). The test was started between 0800 and 0900 h; three blood samples were obtained before and 3 and 24 h after the injection. Dehydroepiandrosterone sulfate (DHEA-S), androstenedione, FSH, LH, estradiol, testosterone, 17-hydroxyprogesterone (17OH Prog), SHBG, and inhibin-B were analyzed in the basal sample. SHBG and testosterone were used to calculate the free androgen index (FAI) as has been previously reported (24). In the 3-h sample, LH and FSH were measured, and in the 24-h sample estradiol, testosterone, 17OH Prog, and androstenedione were determined.

Transabdominal ultrasound was performed by two ultrasonographists with a 5-MHz transducer in Sonoace 6000 C equipment (Madison Co., Seoul, Korea). Ovarian volume was calculated using the simplified formula for a prolate ellipsoid (25). Uterine cross-sectional area was determined using the following formula: uterine length $\times$ uterine anteroposterior diameter (26).

The protocol was approved by the Ethical Committee of the Hospital San Borja Arriarán and the Faculty of Medicine, University of Chile. All parents gave signed informed consent at study entry.

Hormone assays

Serum testosterone, androstenedione, 17OH Prog, DHEA-S, and estradiol were determined by competitive specific binding RIA, and serum LH, FSH, and SHBG were measured by immunoradiometric assays. All kits were supplied by Diagnostic System Laboratories (Webster, TX). Intraassay coefficients of variation were 5.1% for testosterone, 3.2% for androstenedione, 4.2% for 17OH Prog, 3.5% for DHEA-S, 4.1% for estradiol, 6.5% for LH, 3.6% for FSH, and 3.9% for SHBG. Interassay coefficients of variation were 6.4% for testosterone, 6.1% for androstenedione, 5.5% for 17OH Prog, 5.1% for DHEA-S, 6.7% for estradiol, 7.6% for LH, 6.2% for FSH, and 6.9% for SHBG.

Statistical analysis

Results were expressed as mean $\pm$ SEM. Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL). Normality of variables was assessed using the Kolmogorov-Smirnov test. Differences between SGA and AGA groups were assessed by the Student's *t* test for normally distributed variables and nonparametric tests (Mann-Whitney *U*) for nonnormally distributed variables.

To examine the correlations between continuous variables, nonnormally distributed variables were log transformed. Linear correlations were performed and Pearson's correlation coefficients (r) are displayed. $P < 0.05$ was considered statistically significant.

Results

Two hundred seventy girls were examined, of whom 65 (35 AGA, 30 SGA) with a mean chronological age (CA) of 9.7 $\pm$ 0.2 (range 8–12) yr in AGA and 10.2 $\pm$ 0.2 (range 7.83–12.5) yr in SGA (P = ns) and a bone age (BA) of 10 $\pm$ 0.12 yr in AGA and 10.2 $\pm$ 0.16 yr (P = ns) in SGA met the inclusion criteria. Clinical data of recruited girls at study entry are shown in Table 1. By definition, SGA girls were significantly lighter and shorter at birth than AGA girls, even after being corrected for gestational age. At the same pubertal stage, the SGA group of girls had achieved a greater catch-up-growth in weight and height calculated from birth, compared with the AGA group of girls. BMI percentiles and height z-score were within normal ranges in all subjects and

TABLE 1. Clinical characteristics and anthropometric parameters of SGA and AGA groups at birth and at enrollment

	AGA (n = 35)	SGA (n = 30)	*P* value
Newborn period			
Gestational age (wk)	38.6 $\pm$ 0.2	37.4 $\pm$ 0.5 (−)	NS
Birth weight (z-score)	−0.01 $\pm$ 0.12	−1.86 $\pm$ 0.16	<0.001
Birth length (z-score)	0.29 $\pm$ 014	−1.73 $\pm$ 0.18	<0.001
Magnitude of CUG in height	0.14 $\pm$ 0.7	1.5 $\pm$ 0.27	<0.001
Magnitude of CUG in weight	−0.56 $\pm$ 0.21	1.2 $\pm$ 0.33	<0.001
Enrollment			
Height (z-score)	−0.42 $\pm$ 0.19	−0.52 $\pm$ 0.24	NS
Weight (z-score)	0.09 $\pm$ 0.17	−0.3 $\pm$ 0.21	NS
BMI (z-score)	0.4 $\pm$ 0.14	0.24 $\pm$ 0.17	NS
BA to CA ratio	1.02 $\pm$ 0.8	1 $\pm$ 0.76	NS
Waist circumferences	62.4 $\pm$ 4.3	57.5 $\pm$ 5.5	NS
Waist to hip ratio	0.89 $\pm$ 0.01	0.98 $\pm$ 0.01	NS

Values are mean $\pm$ SE. NS, Not significant; CUG, catch-up growth.

did not differ significantly between AGA and SGA girls. In addition, no differences in BA/CA, waist circumference, and waist to hip ratio between both groups were observed.

Pubertal characteristics

No differences in the Tanner staging of pubic hair or the presence of axillary hair/apocrine odor were found between the groups (Table 2).

Hormonal assays

In girls born SGA, a higher basal estradiol level was found, compared with AGA girls. Furthermore, after the GnRH stimulation test, SGA girls had higher estradiol and 17OH Prog (Table 3). Interestingly, a slightly higher testosterone after GnRH was observed in the AGA group. Basal DHEA-S, androstenedione, inhibin-B, FSH, LH, basal testosterone, and FAI were similar in both groups (data not shown). In both groups a positive correlation ($P < 0.001$) between basal testosterone and DHEA-S, androstenedione, and FAI was found. Post-GnRH LH was correlated with basal and post-GnRH estradiol. Furthermore, inhibin-B levels were positively correlated with estrogen levels obtained after the GnRH test ($P < 0.005$). In SGA girls basal LH showed a positive correlation with basal estradiol, 17OH Prog 24 h, and androstenedione and after the GnRH test with basal and post-GnRH test estradiol, basal 17OH Prog, and inhibin-B. In the AGA girls, stimulated 17OH Prog showed a positive correlation with all the measured androgens.

Ultrasound findings

At the beginning of puberty, SGA girls had slightly larger uterine lengths, uterine cross-sectional area, ovarian volume, and number of follicles, compared with the AGA girls. The percent of ovaries with a volume larger than 2 cc was not different between AGA and SGA (62.8 *vs.* 66.6%, respectively, P = ns). A positive correlation was observed between LH and estradiol concentration and average ovarian volume only in the AGA group. In addition, no correlation between the levels of inhibin-B or 17OH Prog and ovarian volume or the number of follicles was found in both groups of girls.

Discussion

Herein we report results of clinical findings, gonadal function, and ultrasonographic uterine and ovarian imaging studies obtained at the beginning of puberty in healthy, age-matched girls born either SGA or AGA. As expected, SGA girls were significantly lighter and shorter at birth than the AGA girls, and these girls achieved a greater catch-up growth in weight and height, calculated from birth, compared with the AGA group.

Interestingly, in this cohort of girls recruited from the community who have a history of SGA, no differences in axillary hair, apocrine odor, or pubic hair as well as ultrasound internal genitalia assessment, compared with age-matched AGA girls, were detected. However, we were able to describe slight hormonal differences between the groups. SGA girls displayed higher basal and post-GnRH estradiol and 24-h 17OH Prog, which has not been reported previously. The clinical relevance of such findings will be evaluated throughout the follow-up of this cohort.

Importantly, androgen levels were within the normal range, and only in the AGA girls, a slightly higher testosterone was observed after the GnRH test. Previous studies indicated that prenatal growth restrain may be followed by exaggerated adrenarche and higher dehydroepiandrosterone/DHEA-S levels (6, 12). However, differences in this pattern of exaggerated adrenarche in other SGA cohorts have

TABLE 2. Pubertal development in AGA and SGA

	Yes (%)	*P* value
Pubic hair		
AGA	64.7	0.137
SGA	57.7	
Axillary hair		
AGA	8.8	0.062
SGA	26.9	
Apocrine odor		
AGA	64.7	0.0801
SGA	57.7	

By χ^2 test.

TABLE 3. Hormonal assessment and ultrasound characteristics of SGA and AGA groups

	Mean ± SE	*P* value
Uterine length (mm)		
AGA	31.2 ± 1.2	
SGA	34.2 ± 2.4	NS
Uterine cross-sectional area (mm^2)		
AGA	320.1 ± 0.57	NS
SGA	383 ± 1.75	
Average ovarian volume (cc)		
AGA	2,5 ± 0.3	NS
SGA	3.1 ± 0.3	
Maximal follicular diameter (cm)		
AGA	7.2 ± 0.53	NS
SGA	6.4 ± 0.68	
LH (μIU/ml)		
AGA	0.71 ± 0.14	NS
SGA	0.79 ± 0.15	
Estradiol (B) (pg/ml)		
AGA	23.9 ± 2.1	0.02
SGA	33.7 ± 3.2	
Estradiol (24 h) (pg/ml)		
AGA	90.8 ± 10.5	0.05
SGA	140.7 ± 15.4	
17OH Prog (B) (ng/ml)		
AGA	0.77 ± 0.07	NS
SGA	0.88 ± 0.08	
17OH Prog (24 h) (ng/ml)		
AGA	1.23 ± 0.22	0.05
SGA	1.3 ± 0.1	
Testosterone (B) (ng/ml)		
AGA	0.44 ± 0.03	NS
SGA	0.36 ± 0.03	
Testosterone (24 h) (ng/ml)		
AGA	0.53 ± 0.05	0.045
SGA	0.41 ± 0.03	
FAI		
AGA	3.5 ± 0.4	NS
SGA	3.3 ± 0.3	

Values are mean ± SE. Student's *t* test and Mann-Whitney *U* test. Statistical significance, $P < 0.05$. NS, Not significant; B, basal levels; estradiol (24 h), 24 h after GnRH test; 17OH Prog (24 h), 24 h after GnRH.

been reported. Indeed, in discordant twins exaggerated adrenarche depends on postnatal weight gain (27), and in other cohorts ethnicity may play a role in the manifestation of exaggerated adrenarche (28–30). In a Dutch cohort of SGA children, the incidence of premature pubarche and the levels of serum DHEA-S levels were reported to be comparable with those of chronological and gestational age-matched AGA controls (31, 32). The discrepancies found in the different studies might be explained by the composition of the SGA children studied. Increased DHEA-S levels have been described in SGA children with catch-up growth, whereas normal levels have been described in those short SGA children receiving GH therapy. Nevertheless, in a French cohort of 20-yr-old women having a history of intrauterine growth retardation, no independent effect on serum androgen concentrations was found, even after adjustment for hormonal contraception (33). In addition, in a Chilean cohort of term SGA children (34) who have been followed from birth until 5 yr of age (our unpublished results) and in a preterm cohort evaluated between the ages of 5 and 7 yr, no differences of DHEA-S levels were found (12, 35). In these reports, the girls studied at the age of pubertal development did not show differences in the levels of DHEA-S. Importantly, SGA girls included in this study did not differ in height and BMI, compared with AGA girls. It remains to be elucidated whether during later stages of puberty they will show differences with regard to DHEA-S levels or other androgen levels. The use of a GnRH test allowed us to demonstrate differences in the gonadotropin and gonadal response patterns during this early stage of pubertal development.

In the ovary, leptin stimulates 17,20 lyase (36) and insulin stimulates 3β- and 17,20 lyase (37). Therefore, the contribution of altered insulin and leptin sensitivity in SGA girls needs future assessment (38–40). In addition, a new signal transduction pathway for LH, which shows a positive cross-talk between insulin and LH at the level of phosphoinositol 3-kinase/AKT pathway in the rat ovary, was demonstrated (41). Again these findings could support the future development of hyperandrogenism in girls born SGA mainly as a decreased insulin sensitivity consequence.

At the onset of puberty, inhibin-B levels were not different in subjects with SGA, compared with the AGA girls, but as expected, in both groups it was strongly associated with estrogen levels. To our knowledge this is the first report that evaluated inhibin-B as a granulose cell hallmark in SGA girls, compared with AGA girls. Because the aim of this research was to follow these girls throughout pubertal development, we may be able to detect whether any difference in this marker is present at a later stage.

The main strength of the present report is that there is no recruitment bias. It remains to be established whether the slight differences in gonadal function pattern of our subjects will persist, disappear, or exacerbate during pubertal development.

In the last century, trends toward earlier pubertal development including earlier menarche in girls in the United States, Asia, and The Netherlands have been documented with stabilization over the last decades (42). Evidence has suggested that the onset of puberty and menarche may be linked to the intrauterine and postnatal growth patterns (43, 44). Importantly both groups had a similar BMI, waist to hip ratio, and fat percent at the beginning of puberty, implying a catch-up growth has been achieved in most of the SGA girls. Furthermore, they do not start with a different body composition at puberty, which has been speculated to alter gonadal function in these girls. However, no longitudinal data on clinical, gonadal function, and ultrosonographic images have been reported in healthy girls followed up throughout pubertal development. Follow-up of this cohort will allow us to understand whether these early pubertal biochemical differences will have an impact in their pubertal tempo and future gonadal function.

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